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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/996,529	11/28/2001	Kimberly A. Gillis	102729-14	3553

21125 7590 05/19/2004

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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/996,529	GILLIS ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *8-10 and 17-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 03/07/02 & 04/10/03
4) ☒ Interview Summary (PTO-413) of 11/24/03 Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of group 3, Claims 1-7, 11-16 in Paper of 03/18/04 is acknowledged and entered.

Claims 1-35 are pending in the instant application and Claims 8-10, 17-35 have been withdrawn from further consideration by the Examiner under 37 CFR 1.142(b) as being drawn to non-elected invention.

Group 3, Claims 1-7, 11-17, ID1 and ID3 markers, are currently under prosecution.

The traversal is on the following ground(s):

1) Applicant asserts that the invention is drawn to measuring the expression levels of ID proteins (e.g., ID-1 and/or ID-3) associated with prostate cancer, wherein the expression level can be monitored by either measuring the nucleic acids associated with ID (e.g., RNA, or DNA), or the ID protein levels. Applicant asserts that MPEP 803.04 states that "nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together". Applicant concludes that accordingly, the Examiner is requested to withdraw the restriction requirement such that mRNA and protein of the 1D1 and ID3 are examined together in this application.

This argument is not found to be persuasive for the following reasons:

It seems that Applicant misinterprets MPEP 803.04 statement that "nucleotide sequences encoding the same protein are not considered to be independent and distinct inventions and will continue to be examined together". It is noted that MPEP 803.04 also teaches that "Nucleotide sequences encoding

different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of 35 U.S.C.121. Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to 35 U.S.C. 121 and 37 CFR 1.141 et seq".

It is further noted that "nucleotide sequences encoding the same protein", e.g. nucleotide sequences that are different by degenerate codon, but encoding the same protein, are not the same as "nucleotide sequences **and the corresponding encoded proteins",** which is the interpretation by Applicant. MPEP 803.04 does not teach that nucleotide sequences and the corresponding encoded proteins are not considered to be independent and distinct inventions and will continue to be examined together.

Thus, it is proper to restrict detecting the protein expression level from detecting mRNA expression level, because the detected nucleotide sequences and the corresponding encoded proteins are structurally distinct, and thus considered independent and distinct, and accordingly, detecting the protein expression level is independent and distinct from detecting mRNA expression level, because they require different method steps, reagents, dosages, and/or schedules used, response variables, and criteria for success. The searches for detecting the protein expression level is not co-extensive with the search for detecting mRNA expression level, and it would be a serious burden for the Examiner to search both methods together.

2) Applicant asserts that the screening methods described by the invention encompass both markers, individually and in combination. Applicant asserts that forcing an election between the two markers, ID-1 and ID-3, is totally unnecessary. Applicant asserts that according to MPEP 803.04, the Commissioner has decided that in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction.

This argument is not found to be persuasive for the following reasons:

It is noted that MPEP803.04 teaches that "up" to 10 distinct sequences could be examined in a single application, and that there is no requirement in MPEP803.04 that more than one sequence has to be examined. The searches for more one sequence are not co-extensive, and it would be a serious burden for the Examiner to search more than one sequence in one single application.

3) Applicant further argues that if based on the requirement for the same methods and reagents, groups (25-48), (1-3), (7-9), (13-14), (17-19), (25-26) should be examined together, despite that there are different objectives.

This argument is not found to be persuasive for the following reasons:

The Examiner did not recite that the restriction is based solely on method steps and reagents. As Applicant pointed out, there are different objectives, besides differences in method steps, dosages, and/or schedules used, response variables, and criteria for success.

4) Applicant further asserts that groups 1-3, 7-9, 13-14, 17-18, 25-26 belong to the same class/subclass 435/6, and thus the search for these groups would be the same.

This argument is not found to be persuasive for the following reasons:

The searches for 1-3, 7-9, 13-14, 17-18, 25-26 are complex, based on different databases, and not just based on classification searches. Therefore, it would be a burden for the Examiner to search all the groups together.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, Group 3, Claims 1-7, 11-17, ID1 and ID3 markers, are currently under prosecution.

OBJECTION

1. Claims 1, 3-7, 16 are objected to because part of claims 1, 3-7, 16 are drawn to non-elected invention, i.e. a method for assessing whether a subject is afflicted with prostate cancer, comprising detecting the presence of a protein expression level corresponding to the marker.

2. Claim 2 is objected to, because it is not clear how the maker "corresponds" to a transcribed polynucleotide.

REJECTION UNDER 35 USC 112, SECOND PARAGRAPH

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 is indefinite because it is drawn to "stringent hybridization conditions". Stringent conditions are not defined by the claim (which reads on the full range of stringent conditions, that is from very permissive to very high

stringency. The specification describes a single non-limiting example of stringent conditions (p.20, lines 17-20). Thus the specification does not provide a standard for ascertaining the requisite degree of stringent conditions and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention and would not be able to determine the metes and bounds of the claims.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, ENABLEMENT

Claims 1-7, 11-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-7, 11-16 are drawn to a method for assessing whether a subject is afflicted with prostate cancer, comprising detecting a significant difference or alteration between mRNA or cDNA level of the ID1 and ID3 markers in a sample and in the control, wherein the markers correspond to transcribed polynucleotides or a portion thereof (Claims 1-2, 11-13, 16). The sample comprises cells or the prostate gland or blood obtained from the subject (claims 3-5). The difference in the level of expression is by a factor of at least about 2 or 3 (claims 6-7). The level of expression of the markers is assessed by amplifying the transcribed polynucleotides, or by detecting the presence of a transcribed polynucleotide, which anneals with the marker or with a portion of the polynucleotide marker, under stringent conditions (claims 14-15).

The specification discloses that the claimed invention provides the use of the inhibitors of Differentiation (ID) proteins, e.g. ID-1 and ID-3, as genetic markers for the detection, diagnosis and prognosis of prostate disorders (p.3). The specification discloses that ID proteins play a role in the regulation of cell differentiation and proliferation, as well as being involved in tumor promotion and angiogenesis, and are a family of four related proteins implicated also in the control and cell-cycle progression (p.3, lines 13-17).

The specification discloses that the gene designated "ID-1" (accession number X77956) or the gene designated "ID-3" (accession number X69111) display a decreased expression level in androgen dependent prostate cancer cell samples (p.9, lines 11-13). The specification discloses how to detect the ID markers (Examples 3-4, on pages 85-86).

A. One cannot extrapolate the teaching in the specification to the enablement of the claims, because **one would not know how to make the invention, due to the lack of disclosure in the claims and in the specification the actual sequence structure of ID-1 and ID-3.**

It is noted that there is no disclosure in the specification what the actual sequence structure of ID-1 and ID-3 polynucleotides is.

One would not know how to identify and make the ID-1 and ID-3 polynucleotides, as defined in the specification, and to carry out the claimed method, based on Genbank sequence numbers, because a sequence from a particular Genbank sequence accession number could be updated, i.e. changed including deletion of several nucleotides, or the accession number could be

removed from Genbank database, due to a request from the inventor of said sequence (see Interview summary with Eric Sayers, a GenBank representative, on 11/24/03). Thus based solely on Genbank sequence accession number, it would not be expected that a polynucleotide sequence based on Genbank accession would remain the same, or available to the public.

Further, the Genbank Accession numbers X77956 and X69111 are essential material for use in the claimed method of detection of prostate cancer. However, incorporation by reference of the Genbank Accession numbers X77956 and X69111 is improper, according to MPEP 6.19, which teaches that incorporation of **essential material** in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. In re Hawkins, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); In re Hawkins, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); In re Hawkins, 486 F.2d 577, 179 USPQ 167 (CCPA 1973) (see MPEP 6.19 and 6.19.01) .

Given that a sequence of a particular Genbank accession number could change or could be removed from the Genbank database, the lack of adequate disclosure in the specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in

the art would be forced into undue experimentation to practice the claimed invention.

B. Further, one cannot extrapolate the teaching in the specification to the enablement of the claims, because **in the absence of objective evidence, one cannot predict that ID-1 and ID-3 polynucleotides have a decreased mRNA expression level in prostate cancer tissue as compared to normal prostate tissue.**

It is noted that although the specification discloses that " the gene designated ID-1 (accession number X77956) or "ID-3" (accession number X69111) displays a decreased expression level in androgen dependent prostate cancer cell samples" (p.9, lines 11-13), there is no actual data showing that ID-1 and ID-3 have a decreased mRNA level in prostate cancer tissue as compared to normal prostate tissues.

It is well known in the art however that mutation or change in the level of expression of a gene is by chance or an unpredictable event, which occurs as the result of normal cellular operations, e.g. mistake during replication or recombination, or interactions with the environment, such as mutagens (Lewin, B, ed, 1983, Genes, Wiley & Son, New York, p. 42, first column, last line bridging second column, p.346, first column, second paragraph). Thus without objective evidence, one cannot predict that ID-1 and ID-3 polynucleotides have a decreased mRNA expression level in prostate cancer tissue as compared to normal prostate tissue.

Further, Keesee et al, 1996, Crit Rev Eukaryotic gene Expression, 6(2-3): 189-214, teach that for a tumor marker to be diagnostically useful, it must be produced by tumor cells, it must be detectable in body fluids and in tissue, it must not be present in healthy individuals or in individuals with benign disease, it must be present in adequate amounts for detection (p.19, column 2, first full para), and it must be highly specific for the tumor target without leading to significant false positive (p.193, column 2, last para). Applicant however has not shown any evidence that the ID-1 and ID-3 polynucleotides have properties required for markers of prostate cancer.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In constrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

Given the unpredictability of the mRNA expression level of ID-1 and ID-3 polynucleotides, the lack of objective evidence or adequate disclosure in the

specification, and in view of the complex nature of the claimed invention, and little is known in the art about the claimed invention, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

C. If Applicant could overcome the above 112, first paragraph rejection, claims 1-7, 11-16 are still rejected under 112, first paragraph for the use of the language "difference in the level of expression" in claim 1, or "the level of expression is significantly altered" in claim 16.

It is noted that "difference in the level of expression" in claim 1, or "the level of expression is significantly altered" **encompasses either an increase or a decrease in the level of expression.**

One cannot extrapolate the teaching in the specification to the scope of the claims, because there is no evidence that the mRNA level of expression of ID-1 and ID-3 polynucleotides is increased in prostate cancer tissue, especially in view that the specification discloses that " the gene designated ID-1 (accession number X77956) or "ID-3" (accession number X69111) displays a decreased expression level in androgen dependent prostate cancer cell samples" (p.9, lines 11-13).

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

D. If Applicant could overcome the above 112, first paragraph rejection, claims 1-7, 11-16 are still rejected under 112, first paragraph for a method for detecting prostate cancer, comprising detecting the mRNA expression level of "a portion" of ID-1 and ID-3 polynucleotides, or comprising detecting the presence

of a transcribed polynucleotide, "which anneals with the marker or with a portion of the polynucleotides CD1 and CD-3 markers under stringent hybridization conditions".

It is noted that a method for detecting prostate cancer, comprising detecting the mRNA expression level of "a portion" of ID-1 and ID-3 polynucleotides **encompasses a method for detecting prostate cancer, comprising detecting the mRNA expression level of unrelated sequences that share a portion with of ID-1 and ID-3 polynucleotides, wherein a portion could be of any size.**

It is further noted that a method for detecting prostate cancer, comprising detecting the presence of a transcribed polynucleotide, "which anneals with the marker or with a portion of the polynucleotides CD1 and CD-3 markers under stringent hybridization conditions" **encompasses a method for detecting prostate cancer, comprising detecting the presence of unrelated sequences that hybridize with ID-1 and ID-3 polynucleotides markers under even the highest stringent hybridization conditions via a common fragment.**

Further, it is noted that stringent conditions encompasses from very low to very high stringent hybridization conditions, wherein under low stringent hybridization conditions, one would expect that unrelated sequence would hybridize to the polynucleotides CD1 and CD-3. For example, Sambrook et al, eds, 1989, 2nd ed, Molecular Cloning, a laboratory manual, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, p. 11.52, teach that the temperature of

hybridization, (which is related to the degree of stringency) should be high enough to suppress hybridization of the probe to incorrect sequences. Sambrook et al further teach that if the probe hybridizes indiscriminately, repeat the hybridization at a higher temperature or wash under conditions of higher stringency (p. 11.52, last two lines).

When given the broadest reasonable interpretation, the claims are clearly intended to encompass a method for detecting prostate cancer, comprising detecting a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the detected or hybridizing molecules encompassed by the claims **would not** share either structural or functional properties with the ID-1 and ID-3 polynucleotides.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

E. If Applicant could overcome the above 112, first paragraph rejection, claims 1-3, 6-7, 11-16 are still rejected under 112, first paragraph for a method for detecting prostate cancer, comprising detecting the mRNA expression level of ID-1 and ID-3 polynucleotides in any sample or any cells.

Claims 1-3, 6-7, 11-16 encompass a method for detecting prostate cancer, comprising detecting the mRNA expression level of ID-1 and ID-3 polynucleotides in any sample or any cells to which prostate cancer has metastasized. .

One cannot extrapolate the teaching in the specification to the scope of the claims. It is unpredictable that metastasized prostate cells still express the

claimed sequences, because expression of a sequence could be lost during the progression toward metastasis. For example, Kibel, AS et al, 2000, J urol, 164(1): 192-6 teach that gene expression in the chromosomal region 12p12-13 is different in primary and metastatic prostate cancer cells, and that inactivation in the chromosome region 12p12-13 occurs prior to metastasis. Zhau, HE, 1994, J Cell Biochem, Suppl 19: 208-216, teach expression of various biomarkers associated with prostate cancer progression. Zhau et al teach that in prostate cancer, PC-3N35 subclones which are cloned from primary and metastatic sites (lymph node, kidney and bone), show difference in the levels of protein expression of various markers, such as c-erbB, vimentin, ICAM-1, cytokeratin, collagen IV between the parental PC-3N35 clone and its metastatic subclones (p.209 and table 1) and that the subline derived from the metastatic site lymph node has a 12p:17q translocation, whereas the bone-derived subline contains an isochromosome 7q (p.211, first column, first paragraph). Cheung S T et al, 2002, Cancer Research, 62(16): 4711-21, teach that from 63 metastatic clones, 39 known genes and 24 express sequence tags are down-regulated, whereas in other 27 metastatic clones 14 known genes and 13 express sequence tags are up-regulated. Ren, C et al, 1998, Cancer Res, 58(6): 1285-90, teach a loss of expression of lysyl oxidase mRNA during progression to metastasis. Gingrich, JR et al, 1996, Cancer res, 56(18): 4096-4102 teach a loss of normal E-cadherin expression as primary tumors become less differentiated and metastasize.

Thus in view of the above, one would not have expected that the claimed sequences are useful for diagnostic information about the presence in a subject of an invasive prostate tumor.

In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, CHRISTINA CHAN can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

MAY 12, 2004